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Retinoblastoma: Result of Radiotherapy

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Radiotherapy result was analyzed in 23 children with retinoblastoma treated in Seoul National University Hospital from 1980 to 1987. Three (17%) had bilateral tumor at diagnosis. Among 20 children with unilateral retinoblastoma 13 children got radiotherapy after enucleation, 2 were treated with radiotherapy alone, and 5 were delivered with radiotherapy after relapse. Of 15 non-recurrent unilateral tumors, there were 5 stage II children, 8 stage III, and 2 stage IV by staging system proposed by St. Jude Children's Research Hospital. Chemotherapy was combined when resection margin of the optic nerve was positive or when malignant cell was found in CSF. Of 12 children who completed radiotherapy, local or distant failure was not found but 2 cases of relapse at the contralateral retina were observed. Their 5 year survival rate was 82.2%. Another case of contralateral relapse was detected in children who was treated with radiotherapy alone. Thus overall frequency of the bilateral disease was 33%. Prognosis of recurrent tumors were so poor that no cases of CR was obtained and that 3 year survival rate was 20%. Two of 3 bilateral cases at diagnosis were in NED status. Complication were sunken orbit only. Result of radiotherapy was so good in early stage or small bulk tumor that treatment delay after diagnosis must not be allowed.

Key Words: Retinoblastoma, Radiotherapy, Tumor bulk.

INTRODUCTION

Retinoblastoma is the most common ocular tumor in children and its incidence varied from 1 in 16,000 to 24,000 live births. Before 4 years of age, 88~95% of patients were diagnosed but diagnosis at birth was not infrequent[1~3].

Bilateral retinoblastoma, synchronous or metachronous, comprised 25~35% of all patients.[1,2,4~9] All the bilateral tumors and 15~20% of the unilateral tumors were thoutht to be hereditary. Therefore retinoblastoma usually occurred sporadically but might show an autosomal dominant inheritance with incomplete penetrance. In case of retinoblastoma genes Rb located in chromosomal region of 13q14, malignant transformation would be associated with loss of function rather than activation as proposed for other oncogenes. So retinoblastoma gave a unique and important clues to human oncogenesis and mutational understanding of embryonic cancer pioneered by Knudson and others[10~13].

The long-term survival increased up to 90% or more by recent studies[5,7], which came from not only development of effective treatment but also the earlier diagnosis and treatment. In Korea, few study was done concerning clinical behaviour, local control and survival by treatment modalities. In order to analyze these factors, results of retinoblastoma patients treated with radiotherapy in Seoul National University Hospital during last 8 years were reviewed.

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MATERIALS AND METHODS

From March, 1980 to August, 1987, total 23 children with retinoblastoma were treated with radiotherapy at the Department of Therapeutic Radiology, Seoul National University Hospital. There were 14 boys and 9 girls. Fifteen children had unilateral tumor at diagnosis and they all were younger than 6 years of age at the time of radiotherapy. Initial treatment was delayed after diagnosis in 4 of them (Table 1). Three children, 2 boys and a girl, had bilateral tumors at diagnosis and their symptoms were first noted within 1 month after birth. Ages at treatment was 1, 2, and 27 months after birth. But case associated with family history was not found. Five children had recurrent tumors on the ipsilateral orbits at 2 to 5 months after enucleation of unilateral tumors, and all were older than 3 years of age at time of radiotherapy. The mean interval between the first symptom and

Table 1. Stage versus Age at Treatment Among the Unilateral Retinoblatoma at Diagnosis

Age (Months)	II	III	IV	Total
– 12	2	2	–	4
13 – 24	2	2*	–	4
25 – 36	1	2#	1@	4
37 – 48	–	1*	1	2
49 – 60	–	–	–	–
61 – 72	–	1	–	1
Total	5	8	2	15

* : Each inculuded a case with treatment delay after diagnosis.
\# : delayed enucleation and incomplete radiotherapy
@ : incomplete radiotherapy alone

Table 2. Staging System of Retinoblastoma Proposed by St. Jude Children's Research Hospital[14]

Staging
I. Tumor (unifocal or mutifocal) confined to retina
II. Tumor (unifocal or multifocal) confined to globe
– with vitreous seeding
III. Extraocular extension of tumor (regional)
– extending beyond cut end of optic nerve (including subarachnoid extension)
– extending into orbital contents
IV. Distant metastasis
– extending through optic nerve to brain
– blood-borne metastasis

diagnosis was 3.6 months in non-recurrent children.

As for the staging, almost all tumors were so advanced by Reese-Ellsworth staging system, that is, stage V except one of stage IV, that we decided to adopt the staging system proposed by St. Jude Children's Research Hospital to differ the tumor extent more clearly.(Table 2)[14] Excluding bilateral and recurrent tumors, there were no stage I (retinal), 5 stage II (global), 8 stage III (orbital), and 2 stage IV (cranial or metastatic) tumors. Correlation of age of treatment with stage showed that the younger the children the less advanced the stage. In bilateral tumors, enucleated tumors were stage II-III but remained tumors were all stage I. The initial stage of 5 recurrent tumors of which stage could be assessed ranged from I-III. But at the time of radiotherapy, 4 had stage III and one had stage II if restaged. Among the 15 children with unilateral tumor, 13 had enucleation and radiotherapy and 2 received radiotherapy alone. The more advanced tumor in the bilateral tumors were enucleated in 2 children and enucleated and irradiated in 1 children while less advaced tumor was treated with radiotherapy only in 3 three among 5 recurrent tumor had surgical treatment before rediotherapy, 1 with partial resection and 2 with exenteration.

Co-60 gamma ray or electron beam was delivered with one anterior port or two wedged anterior oblique ports to enucleated case and with one lateral port to non-enucleated tumors. Total dose was 28~50 Gy for the enucleated, 36~45 Gy for the non-enucleated, and 30~46 Gy for the recurrent. Fractionation schedule was 3~4 Gy/fractions with 3 fractions per week before 1984, and was conventional with daily dose of 2 Gy after then. Conventional fractionation schedule was used for the recurrent and stage III-IV cases except one with stage III. TDF ranged from 82~97 and its median was 79.5. In the unilateral tumors, median TDF for stage II was 79.5 and TDF for stage III ranged 82~97. TDF for the bilateral was 79.5~85 but had wide range of 62~92 for the recurrent. When malignant cell was detected in the cerebrospinal fluid whole brain was also irradiated with 24~30 Gy using lateral ports. Chemotherapy was combined to radiotherapy in 4 enucleated children whose CSF or resection margin of the optic nerve was positive or whose tumor stage was IV and also in 2 children with recurrent tumors. Chemotherapy consisted of systemic treatment (cyclophophamide, vincristine, and adriamycin) and intrathecal treatment (methotrexate alone or combined with Ara-C and solucortef). Survival was calculated with the life table method[15] and comparison of survival was done by the log rank test[16].

RESULT

One of 13 children with enucleated unilateral tumor did not complete radiotherapy but continued insufficient chemotherapy at other hospital and died of intracranial extension and skull base destruction at 15 monthes after diagnosis (Table 3). Among 12 children with complete radiotherapy

Table 3. Treatment and End Results of 15 Unilateral Retinoblastomas

Case #	Stage	Optic nerve margin	Treatment method	Relapse	Result
1	II	?	E + RT		92M NED
2	II	Negative	E + RT		88M NED
3	II	Negative	E + RT		77M NED
4	II	Negative	E + RT		72M NED
5	II	?	E + RT		17M NED
6	II	?	RT		42M DwD
7	III	Negative	E + RT		69M NED
8	III	?	E + RT	Contra.	5M DwD
9	III	Positive	E + RT	Contra + LN	8M DwD
10	III	Positive	E + RT + CT		3M NED
11	III	Positive	E + (RT + CT)	Cranial	15M NED
12	III	Positive	E + RT + CT		61M NED
13	III	Positive	E + RT + CT		13M NED
14	IV	Positive	E + RT + CT		14M NED
15	IV	?	(RT)		1M DwD

E : Enucleation, RT : Radiotherapy, CT : Chemotherapy, ( ) : Incomplete or insufficient treatment, Contra. : Relapse on contralateral retina, LN : Lymph node, Cranial : Relapse in the brain, NED : No evidence of disease, DwD : Died with disease

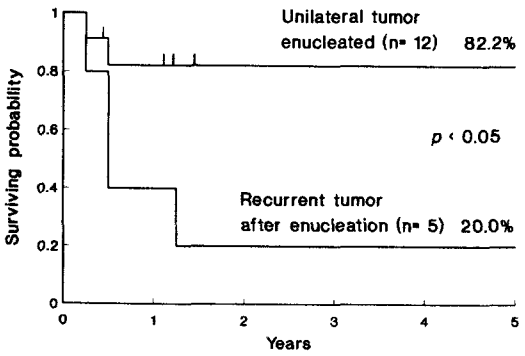

Fig. 1. Survival of unilateral retinoblastoma patients who were treated with enucleation followed by radiotherapy and of the retinoblastoma patients who were treated with radiotherapy with or without mass resection after tumor relapse after enucleation alone. Survival of the recurrent cases were significantly poor.

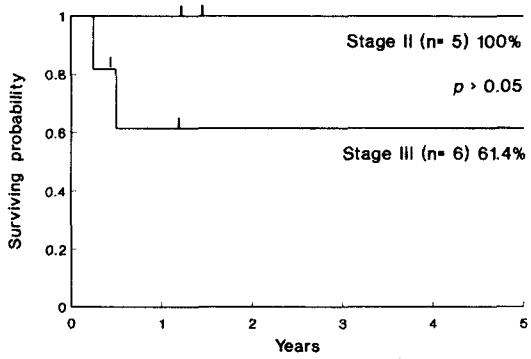

Fig. 2. Survival of unilateral retinoblastoma patients by the tumor stage according to St. Jude Children's Reseasch Hospital at the time of radiotherapy.

there were no local or distant failure but 2 cases of contralateral relapses (17%), both of them were stage III, at 3.5 and 4.5 months after enucleation. One case of contralateral relapse was also combined with regional relapse at the subdigastric lymph node on both sides at the same time. The second course of radiotherapy was tried to one with contralateral relapse but failed to control tumor. They all died at 1.5 and 3.5 months after contralateral relapse. The 5 year survival rate of 12 children was 82.2% (Fig. 1).

All of 5 children with stage II have veen in the disease-free status and 3 of them survived 6 years. In stage III, meanwhile, 4 of 6 children have been in disease-free status and 2 of them survived 5 years. Survival at 5 years with stage II and III was 100% and 61.4%, respectively, but their difference was not significant (Fig. 2). Survival was slightly influenced

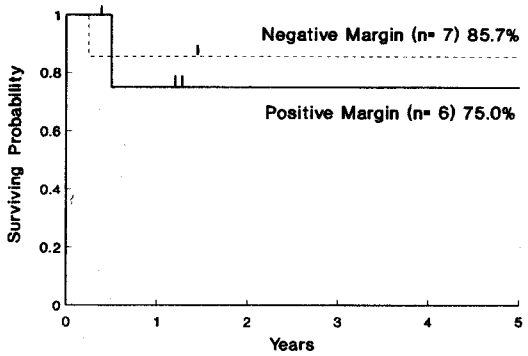

Fig. 3. Survival of unilateral retinoblastoma patients by the status of tumor involvement at the resection margin of the optic nerve.

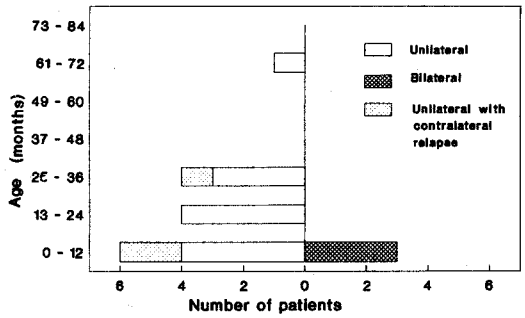

Fig. 4. Pattern of bilateral retinoblastoma at diagnosis or resulting from contralateral relapse of unilateral tumor by the age when the first symptoms were observed.

by the status of resection margin of the optic nerve (Fig. 3). One of the 5 children with positve resection margin survived 5 years but 5 among 7 children with clear resection margin survived 5 years. Also total radiation dose or fractionation schedule did not affected the survival. Survival at 5 years with TDF>80 and TDF<80 was 67.7% and 100%, respectively. ($p>0.05$) Survival with conventional fractionation and with high fraction size with unconventional schedule was 66.7% and 100%, respectively ($p>0.05$).

Of 2 children with unilateral tumor treated with radiotherapy alone, one with intracranial extension (stage IV) did not complete radiotherapy and died of tumor at 1 months after diagnosis. The other child whose response was not evaluated because of vitreous turbidity had relapse on contralateral retina, although exact date of relapse could not be confirmed, died at 42 months after radiotherapy, too.

Among 3 children with bilateral tumors, one had partial remission and 2 had complete remission. The child with PR was then enucleated again and the second course of radiotherapy but seemed to have intracranial extension at 2 months after enucleation and was lost to follow-up. One CR child developed a new lesion on the ipsilateral retina adjacent to the primary mass and the second course of radiotherapy cured of tumor. Another child has been followed up with disease-free status.

When, thus, unilateral and bilateral cases were pooled together, frequency of the bilateral retinal involvement was 33% (6/18). Three of them was confirmed at diagnosis and other 3 was observed during follow-up period to have contralateral relapse. The frequency of bilateral disease was 55.6% (5/9) when the first symptom were detected within 12 months after birth while was 11.1% (1/9) after 12 months of age (Fig. 4).

Of 5 children with the recurrent tumor, treatment response was poor; there was no complete remission, 1 partial remission, 1 minimal remission, and 2 progression of disease. Regional disease progression to the ipsilateral posterior cervical lymph node in 1 children and to the adjacent and distant skull bones in another child was observed during radiotherapy. Their 5 year survival rate of 20% was of course markedly lower than that of children with unilateral tumor enucleated and irradiated (Fig. 1). Four of them died within 15 months after radiotherapy and the remaining one child whose tumor progressed during radiotherapy was found alive after chemotherapy without documentation of disease status. His interval of 15 months between the initial enucleation and relapse was longer than those (3, 5, 6, and 8 months) of other 4 children.

There was no cataract in the treated or contralateral eyes. The sunken orbit by orbital fat atrophy was observed in 4 chlidren among 8 children who survived 5 years, but the degree of fat atrophy was mild in 3 of them. Symblepharon was also combined with the sunken orbit in a child. Other 3 children did not show grossly abnormal orbit and the other one could not be assessed. There was no retinopathy, optic nerve injury, or second malgnant neoplasm.

DISCUSSION

The 5 year survival of 82.2% in enucleated unilateral tumors was in the previously reported survival ranges from 73% to 93%[3,4,5,6,7,17,18].

Better survival of enucleated unilateral retinoblastoma than that of ipsilaterally recurrent retinoblastoma after enucleation was possibly caused by tumor burden at the time of radiotherapy, because recurrent tumors extended to orbital tissue and had gross bulky tumor though some of recurrent tumors were partially resected or exenterated. This seemed to delineate the efficacy of radiotherapy in the management of retinoblastoma or simply confirmed what radiotherapy must not be delayed till tumor relapse after enucleation.

When tumors which were delivered with full radiation dose were grouped into large or small bulk by their mass size at the time of radiotherapy, enucleated unilateral tumors and tumors in intact eyes among the bilateral cases belonged to small bulk tumor (microscopic residual or atage I) and unilateral tumors those were not enucleated and the recurrent tumors comprised large bulk tumors (stage III-IV). Local control was obtained in 14/15 and 1/6 in small and large bulk tumors, respectively and 5 year survival rates were 76.4% in small bulk tumors and 3 year survivial rate was 33.3% in large bulk tumors, (one was followed up for 39 months.)

Better treatment result in the small bulk tumor was reported by Cassady et al[6] and local control was 49% but that of stage I-III and IV-V by Reese-Ellswoth staging were 73% and 23%, respectively. Tumor extent expressed as other parameter than the stage also associated to treatment result. Mortality rate was 72~80%, 60~62%, and 43~85% in tumors involving sclera, choriod, and epibulbar tissue, respectively[4]. Survival rate was 100% when there was no tumor involvement at the resection margin of the optic nerve and sclera while survival was 34% when there was tumor involvement at either of two structures[8], and was greater than 90%, 67~70%, and 0% in single or retinal tumors, tumors with intraocular spresad or involving the optic nerve, and extraocular tumors, respectively[5]. But in Stanford series[19], local control and eyeball saving rate without secondary enucleation was 18/21 and 80% in 21 stage I-III patients and 14/17 and 30% in 17 stage IV-V patients, which suggested the better eyeball saving even if local control was not affected by tumor stage.

In enucleated small bulk tumors, no influence of any parameters to survival or local control thought be resulted from overall good result or small number of cases. But no difference of survival by the status of resection margin of the optic nerve and by the stage might suggest the beneficial effect of chemotherapy because large proportion of stage III children with positive resection margin was treated with combined therary. Among 3 children treated with enucleation and radiotherapy, two children (one had positive margin but status of another was unknown) died after contralateral relapse, and all of 4 children who had chemotherapy were in NED state. It might be too soon to conclude that chemotherapy effect was positive for children with positive resection margin at the optic nerve because 2 of them were not followed up over 14 months and 1 of them was lost to follow-up at 3 months.

Bilateral involvement of 33%, be it synchronous and metachronous, among children from whom 5 recurrent cases were excluded was well in the range of reported frequencies of 20~35%.Its close correlation with the age when the first symptoms were noticed again reminded us of the hereditary nature of the bilateral retinoblastoma. In Oxford series, slight better survival at 4 years in bilateral disease (87.4% vs 84.5%) was analyzed to be affected by higher proportion of younger age in bilateral disease based on that children diagnosed under age 1 were well likely to have a tumor in a less advanced stage than were the older children[5]. It has been confusing that survival of the bilateral disease was reported to be better than[8], equal to[5,14], or worse than[4] that of the unilateral disease, but we think the important parameter for prognosis is not the laterality of tumor itself but the stage of the tumor at diagnosis. Analysis by the stage of each tumor will clarify the importance of the tumor bulk or stage of the retinoblastoma. Therefore survival of 2/3 in 3 synchronous bilateral disease in this analysis was not meaningful itself.

The interval between the first symptom and diagnosis was reported as an important prognostic factor in some studies. Tumor rapidly advanced in its extent during symptom duration of 6-12 months and thus extraocular tumor consisted of major proportion of tumor thereafter in a report from Colombia where incidence of retinoblastoma was very high, the second most common childhood tumor[9].

Parental objection of recommended enucleation after diagnosis delayed treatment in 3 children with unilateral presentation and 2 of them also did not finished the treatment as planned and all died. Among the recurrent tumor, one case had treatment delay of 26 months while he was diagnosed at 11 months old. Exact cause of delay was not known but we assume that parental fear of enucleation of

their son might play the major role. From our result and others[5,17], it is highly probable that he would have survived if he were adequately treated without delay after diagnosis. Thus, like all other tumors, early diagnosis and immediate adequate treatment without delay after diagnosis will result in long-term survival and high probability of preservation of vision.

Of the local treatment modality for the retinoblastoma, only radiotherapy effectively treat the whole globe including the subclinical tumor and vitreous seeding. Irradiation of the entire retina was founded on the assertion that whole retina is at risk[20] and that etiology of bilateral disease is not contralateral spread via the optic nerve but multifocal oncogenesis[9]. A report that separate tumor foci were detected at the periphery of the primary tumor in 64% of unilateral retinoblastoma showed the magnitude of multiplicity[21].

By external radiotherapy Cassady reported that tumor control was not improved with higher dose above 35 Gy with dose per fraction ranged from 333-400 cGy[6]. But dose levels up to 52 Gy with conventional fractionation were said to give a low risk for developing retinal vascular disturbances[22]. The shape of sigmoid dose-response (retinal injury) curve was apparently steep between 50 and 60 Gy, and then it was recommended that all fields should be treated daily with fraction size of 180-190 cGy[23]. Thus no difference of survival or control by dose expressed in TDF in small bulk tumor seemed to be extraordinary. Modification of usual teletherapy technique consisted of a single lateral port was developed to deliver an acceptable dose distribution to the entire retinal surface including ora serrata[24], and survival using one of this modified techniques was better than that using other lens sparing technique in the small bulk tumors with intact eyeball[7].

Advocates of focal radiotherapy using ^{60}Co applicator reported that treatment result was not different from that with teletherapy and that focal radiotherapy could be indicated and well suited for single or multiple tumors up to size of 10~13 mm in diameter[22,25]. There remained the chance of relapse at periphery of the primary tumor site as mentioned that 50% radiation therapy failures were adjacent to the original lesion and the other 50% appeared at a new retinal site[24], and this size of tumor could be well controlled with teletherapy. Sequelae such as 'Dry-dry' syndrome, corneal dystrophy, cataract, conjunctivitis, retinal damage made refinement of the treatment technique and tended to discontinue the use of cobalt plaque[23,26].

Chemotherapy that was apparantly effective in stage III tumor with positive resection margin at the optic nerve in our patients was suggested to be considered for tumors involving more than 25% of the retina, large stage I-II nonenucleated tumors, extensive tumors involving choroid, or the extraocular tumors[14]. It must be, however, reminded that loss of vision, major clinical difficulties with eyesight, and complication were much more frequent when chemotherapy was used in conjunction with radiotherapy[27] and that all patients with advanced tumor were failed to be controlled with operation and chemotherapy, although single drug was used, without radiotherapy[28].

Patients with retinoblastoma, especially genetic form, had a substantial risk of developing second malignant neoplasm inside or outside of the radiotherapy field or in patients without radiotherapy[3,5,28~34]. Cumulative incidence rates of second tumors were reported as 4.2% after 18 years among 882 patients and 8.4% for 384 patients with genetic form[32]. Among 1,093 patients, 80 patients deveolped the second tumors and 78 of 80 tumors were from bilateral tumors; thus 12.6% of survivors of bilateral tumors developed the second cancer and seventy-one percent of patients developed the second cancer in the radiation fields[31]. Suggestion that cyclophosphamide might increase the risk of sencond primary cancer in patients with genetic retinoblastoma[32], must be taken into account in planning treatment.

In summary, radiotherapy result for retinoblastoma is good and further increase in survival with better quality of vision could be obtained by early diagnosis and adequate, definite treatment without delay. Overcoming of parental objection to treatment is necessary for the immediate treatment and genetic counselling and examination of newborne, infant, or children whose family had retinoblastoma patients[35,36] is necessary for the early diagnosis.

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= 국문초록 =

망막아세포종의 방사선치료 성적

서울대학교 의과대학 치료방사선과학교실

김 일 한·김 종 훈·박 찬 일

1980년 3월부터 1987년 8월까지 서울대학교병원 치료방사선과에서 망막아세포종으로 방사선 치료를 받았던 23예의 치료 성적을 보고한다.

20예의 편측성 종양에서, 13예는 안구적출술후 방사선치료를, 2예는 방사선치료만, 5예는 안구적출후 동측 재발종양의 방사선치료를 받았다. 재발성 종양을 제외한 15예의 병기는 St. Jude Children's Research Hospital의 병기분류 기준에 의한 I기(retinal)는 없고, II기(global) 5예, III기(orbital) 8예, IV기(cranial or metastatic) 2예였다. 양측성 종양 3예는 생후 1개월 이내에 증상이 나타났고, 진행된 종양측은 안구적출술을 시행했으며 조기 종양측은(3예 모두 I기) 방사선 치료를 하였다. 시신경 절단부 또는 뇌척수액에서 종양 세포가 확인된 경우에는 항암화학치료를 병용하였다.

수술후 계획대로 방사선치료를 받은 12예의 5년 생존율은 82.2%이며, 국소재발 또는 원격전이는 없었으나, 2환아(III기)의 진단시 무병상태였던 반대측 망막에서 종양이 속발하였다. 일차적 방사선치료를 계획대로 받은 1예의 반대측 망막에서 종양이 속발하였다. 따라서 양측성 종양의 전반적 빈도는 33%였다. 재발성종양 5예의 치료성적은 매우 불량하여 생존율은 20%였다. 양측성 종양 3예중 2예가 무병상태로 생존하고 있다. 방사선 치료후의 변화로는 안와 연조직 위축이 관찰되었다.

방사선 치료성적은 조기 병기 또는 종양의 크기가 작은 경우에 양호하여 조기 치료가 중요하며 진단후 치료가 지연되지 않도록 함이 중요하다.